REMARKS

Amendments to the claims

Claims 1-41 are pending. Claims 11-12, 18-19, 22, 31, 35, 37, and 41 have been canceled without prejudice. Applicant reserves the right to pursue the subject matter of these claims in a continuing application. New claims 42-49 have been added. Accordingly, claims 1-10, 13-17, 20-21, 23-30, 32-34, 36, 38-40, and 42-49 will remain after entrance of the present Amendment.

Independent claim 1 has been amended to clarify that the claimed method involves using a spectrometer to acquire a spectrum of amniotic fluid *in situ*. The acquired spectrum is then processed to predict a risk of developing a medical condition based on a predetermined correlation between spectra of amniotic fluid and the likelihood of developing said medical condition (e.g., see Abstract and paragraphs [0035] to [0056] and [0059] of the specification).

Independent claim 6 has been re-written as dependent from claim 1.

Independent claims 16 and 30 have been amended to clarify that the claimed method and apparatus involve using an optical or magnetic resonance spectrometer to acquire a spectrum of amniotic fluid (e.g., see original claims 19 and 21 for support). These claims apply to *in situ* or *ex vivo* situations. The acquired spectrum is then processed to predict a risk of developing a medical condition based on a predetermined correlation between spectra of amniotic fluid and the likelihood of developing said medical condition (e.g., see Abstract and paragraphs [0035] to [0056] and [0059] of the specification).

A number of dependent claims have been amended to correct inadvertent and obvious errors and to harmonize the claims in accordance with the aforementioned amendments, e.g., to maintain proper antecedent basis and/or to maintain proper dependencies.

New claim 42 finds support, e.g., in original claim 20.

New claim 43 finds support, e.g., in paragraphs [0058] and [0068] of the specification.

New claims 44 and 46 find support, e.g., in paragraphs [0040] and [0059] of the specification.

New claim 45 finds support, e.g., in original claim 2.

New claims 47 and 48 find support, e.g., in paragraph [0057] of the specification.

New claim 49 finds support, e.g., in paragraph [0062] of the specification.

No new matter has been added.

Rejection of claims 1, 3-19, 22-31 and 35-41 under 35 U.S.C. § 103(a)

Claims 1, 3-19, 22-31 and 35-41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Walker (US 6690958) in view of Rosenfeld (US 7191068). Applicant respectfully traverses this rejection.

As amended, the claims relate to methods and apparatuses that use a spectrometer to acquire *spectra* of *amniotic fluid* and then use these spectra to predict the likelihood that the pregnant mother or her offspring will develop a medical condition. This prediction is based on the spectra and a predetermined correlation between spectra of amniotic fluid and the likelihood of developing the medical condition. As discussed in the specification, this spectral correlation approach is different from methods that rely on correlations based on individual identified biomarkers (e.g., see Abstract). In order to establish a *prima facie* case of obviousness, the Examiner needs to demonstrate that the combined teachings of Walker and Rosenfeld produce the claimed invention. The Examiner has failed to meet this burden.

In particular, the Examiner claims that Walker discloses "an optical probe system and method for analyzing body *fluids* including *amniotic fluid* where the probe head or optical coupler is positioned against the mother's skin with respect to the amniotic sac and obtaining ultrasound images" (*emphasis* added). This is incorrect. The teachings of Walker are solely and explicitly directed to the analysis of body *tissues* such as the fetal brain, not body *fluids* such as amniotic fluid. Thus, in the "Summary of the Invention" section, Walker states (with emphasis added):

> [...] In one aspect, the need for a method to precisely position the NIRS optical sample volume in *tissue* is met by ultrasound guided near infrared spectrometry.
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> In another aspect, a catheter includes optical sources, a photodetector, ultrasound transducer array, and stabilization balloon. The display shows an optical sample volume through *tissue of interest* that is superimposed over the ultrasound image, and an oxygenation indicator.
>
> In another aspect, the diagnostic apparatus includes a near infrared spectrophotometer

> that measures *tissue* oxygenation in an optical sample volume and an ultrasound imager to accurately position the optical sample volume in biological *tissue or vessels*. [...]
>
> In some embodiments, the optical source and photodetector are attached to rotary and linear sensors that supply position data, for example to processing element such as a computer, processor, controller, logic element, or the like. The processing element can calculate the distance between the optical source and the photodetector. The source-detector distance and tissue optical properties based on near infrared spectrophotometer measurements determine the position of the optical sample volume in the tissue. Calibration fixtures or phantoms that have optical properties similar to the *tissue of interest* can be used to determine the shape of the optical sample volume for a particular source-detector distance.
>
> In another aspect, some systems may include an electronic graphics display and a processing or control element that superimposes an experimentally-determined optical sample volume over an ultrasound image on the display. The combined optical sample volume and ultrasound image display enables a clinician to use the electronic display to accurately position the optical sample volume through a desired *tissue* portion.
>
> In operational aspects, the diagnostic apparatus is capable of performing a noninvasive method of precisely positioning a optical sample volume projected and received by a near infrared spectrophotometer (NIRS) in deep *tissue* through usage of an ultrasound imager. An example of the positioning method includes several actions such as arranging an optical source, a linear array of ultrasound transducers, and an optical photodetector in the one plane so that the ultrasound sample volume intersects the optical sample volume. An outline of the theoretical optical sample volume is superimposed over the ultrasound image on an electronic graphics display. The superimposed image on the electronic graphics display enables or facilitates the capability of a clinician to accurately position the optical sample volume through the desired *tissue*.
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> Various embodiments and examples of the diagnostic apparatus can be used for different tasks. A *tissue* analysis device, for example capable of taking measurements through the skin, can be used for functions such as noninvasive detection of fetal hypoxemia. A catheter device can be used for functions such as noninvasive determination of oxygenation level in *tissue* through vessels and body openings including but not limited to oral, rectal, nasal, and otic openings. For example a catheter may be used to establish whether oxygenation is sufficient for the heart to be successfully resuscitated by defibrillation.

In accordance with this summary, the devices and methods of Walker are all designed to measure optical absorption caused by body *tissues*, e.g., see the system of Figure 4 where Walker displays "Patient Tissue" between optical source 402 and detector 404 (see also discussion in column 7, lines 36-56). The only mention in Walker of the words "amniotic fluid" occur in the following section (with emphasis added) which discusses the use of the fetal tissue calibration phantom of Figure 9:

> During measurements of actual biological tissue, photons emitted from the optical source pass through the abdominal wall, *amniotic fluid*, fetal brain, *amniotic fluid*, and the abdominal wall layers. Components of the tissue phantom have similar optical properties of absorption, scattering and index of refraction in comparison to actual tissue except for the fetal brain sphere. The fetal brain sphere has a cylinder of low absorptive material surrounded by high absorptive material. The trans-abdominal fetal tissue calibration phantom 900 includes the inner vesicle 902 that approximates characteristics of the fetal brain sphere. The trans-abdominal fetal tissue calibration phantom 900 includes the outer region 904 that approximates characteristics of the abdominal wall and the *amniotic fluid*. A centerline 906 of the inner vesicle cylinder 902 is parallel to the optical path of the photons at the deepest point of the sample volume.
>
> The optical-acoustic diagnostic apparatus is calibrated by determining the source-photodetector distance where the optical sample volume is positioned in the low absorption cylinder of the brain sphere. The source-photodetector distance that results in the optical sample volume being positioned in the low absorptive cylinder of the brain sphere is experimentally determined. The calibration procedure begins with a very short source-photodetector distance. The photodetector signal is low as the beam passes completely through the abdominal wall layer and increases through the *amniotic fluid* layer. The photodetector signal then decreases as the beam passes through the high absorptive section of the fetal brain sphere and increases as the beam continues through the low absorptive center cylinder of the fetal brain sphere. The photodetector signal decreases as the beam passes through the deeper high absorptive section of the fetal brain sphere.

A person of ordinary skill would immediately recognize that this section describes how the Walker device can be calibrated prior to analyzing fetal brain *tissue*. While the Walker method may well require that radiation pass through amniotic fluid (and the abdominal wall) on its way in and out of the fetal brain tissue, it is readily apparent that Walker does not teach methods or apparatuses that acquire and process spectra of *amniotic fluid* to predict the likelihood that the pregnant mother or her offspring will develop a medical condition. Thus, while Walker describes methods in which ultrasound images are used to confirm that radiation *is* passing through a desired tissue (e.g., see column 2, lines 58-65, "[t]he combined optical sample volume and ultrasound image display enables a clinician to use the electronic display to accurately position the optical sample volume through a desired tissue portion"), the present application describes methods in which ultrasound images are used to confirm that radiation *is not* passing through an undesired tissue (e.g., see paragraph [0057], "[i]t will be appreciated that ultrasound images of the amniotic sac may be used to help arranging the probe to direct or confirm that the probe will measure the amniotic fluid without interference of the fetus").

Rosenfeld does not remedy the deficiencies of Walker. Rosenfeld teaches invasive methods in which amniotic fluid samples are removed from pregnant individuals (e.g., by amniocentesis, see column 17, lines 3-11, 25-31 and 56-61). The extracted samples are then processed to separate and/or concentrate components (e.g., by gel electrophoresis, HPLC fractionation and protein digestion, see column 20, lines 15-67 and column 22, line 59 to column 23, line 3). In this context, the Examiner is reminded that the claimed methods are directed to methods in which the amniotic fluid is analyzed *in situ* (e.g., see claim 1) or without processing the amniotic fluid to separate or concentrate its components (e.g., see claim 16). Either way the methods are performed without altering the composition of the amniotic fluid. Finally, in Rosenfeld, mass spectra of the *processed* amniotic fluid samples are obtained *ex vivo* and used to identify individual protein biomarkers that correlate with certain intrauterine conditions (see column 23, line 4 to column 27, line 30). In light of this, the Examiner's statements that Rosenfeld teaches "non-invasive" methods in which "[t]he spectrometer is arranged with respect to the amniotic sac to measure amniotic fluid in situ wihout insertion of any instrument into the amniotic sac" are quite puzzling and clearly incorrect. The Examiner has also failed to explain how one skilled in the art would "use the teachings [of Rosenfeld] to modify [Walker]." Walker teaches a non-invasive method that uses infrared spectroscopy to analyze tissues *in situ*. Rosenfeld teaches an invasive method that uses mass spectroscopy *ex vivo* to identify individual protein biomarkers in amniotic fluid that has been extracted from the mother and subsequently processed to separate and/or concentrate components. While the two approaches might complement each other when used in parallel, Applicant fails to see how one could *modify* one in view of the other, let alone how such a modification would lead the skilled person to the claimed inventions. Clarification or withdrawl of this rejection is therefore respectfully requested.

Rejection of claims 2, 20, 32 and 33 under 35 U.S.C. § 103(a)

Claims 2, 20, 32, and 33 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Walker in view of Rosenfeld, as applied above, and further in view of Khoury (US 6618138). Applicant respectfully traverses this rejection.

The deficiencies of Walker and Rosenfeld are discussed above. Khoury describes a "spatial fluorescence spectroscopic association memory-correlator" (see column 1, lines 57-59).

The system can be used in conjunction with a Raman spectrometer (see column 2, lines 46-47). The Examiner cites Khoury in order to provide certain limitations found in dependent claims 2, 20, 32, and 33 (use of Raman spectrometer) and states that "it would have therefore been obvious to one of ordinary skill in the art to use the teachings by [Khoury] to modify Walker and [Rosenfeld] such that the markers in the amniotic fluid flowing through the abdominal wall are analyzed in a fast and efficient manner for the recognition of materials or compounds that are indicative of birth disorders." Again, the Examiner fails to explain how one would actually modify Walker and Rosenfeld based on the teachings of Khoury. As noted above, it is unclear how one skilled in the art could even combine the teachings of Walker and Rosenfeld. Accordingly, even if we assume *arguendo* that the skilled person would be motivated to add in the teachings of Khoury, we are only left with two options, namely modifying Walker in view of Khoury or modifying Rosenfeld in view of Khoury. Even if these modifications had been successful, neither one would have produced the claimed invention. Indeed, if the skilled person replaced the near infrared spectrophometer of Walker with the Raman-based apparatus of Khoury, the product would still be a device that analyzes body *tissues*. If the skilled person replaced the mass spectrometer of Rosenfeld with the Raman-based apparatus of Khoury, the product would still be a device that identifies individual protein biomarkers in amniotic fluid that has been extracted from the mother and subsequently processed to separate and/or concentrate components. Since the combined teachings of Walker, Rosenfeld and Khoury fail to produce the claimed invention, the Examiner has failed to establish a *prima facie* case of obviousness. Applicant respectfully submits that the rejection should therefore be withdrawn.

Rejection of claims 21 and 34 under 35 U.S.C. § 103(a)

Claims 21 and 34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Walker in view of Rosenfeld, as applied above, and further in view of Ebbels (US 6683455). Applicant respectfully traverses this rejection.

The deficiencies of Walker and Rosenfeld are discussed above. Ebbels describes methods for identifying analytes including biomarkers in complex fluids using magnetic resonance spectroscopy (see column 9, lines 19 to column 11, line 33). The Examiner cites Ebbels in order to provide certain limitations found in dependent claims 21 and 34 (use of

magnetic resonance spectroscopy) and states that "it would have therefore been obvious to one of ordinary skill in the art to use the teachings by [Ebbels] to modify Walker and [Rosenfeld] such that significant markers/analytes found in amniotic fluid may be measured for effective diagnosis of birth disorders or abnormalities." Yet again, the Examiner fails to explain how one would actually modify Walker and Rosenfeld based on the teachings of Ebbels. As noted above, it is unclear how one skilled in the art could even combine the teachings of Walker and Rosenfeld. Accordingly, even if we assume *arguendo* that the skilled person would be motivated to add in the teachings of Ebbels, we are only left with two options, namely modifying Walker in view of Ebbels or modifying Rosenfeld in view of Ebbels. Even if these modifications had been successful, neither one would have produced the claimed invention. Indeed, if the skilled person replaced the near infrared spectrophometer of Walker with the magnetic resonance spectrometer of Ebbels, the product would still be a device that analyzes body *tissues*. If the skilled person replaced the mass spectrometer of Rosenfeld with the magnetic resonance spectrometer of Ebbels, the product would still be a device that identifies individual protein biomarkers in amniotic fluid that has been extracted from the mother and subsequently processed to separate and/or concentrate components. Since the combined teachings of Walker, Rosenfeld and Ebbels fail to produce the claimed invention, the Examiner has failed to establish a *prima facie* case of obviousness. Applicant respectfully submits that the rejection should therefore be withdrawn.

Conclusion

In view of the above Amendment and Remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the outstanding rejections. Favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited. It is believed that all fees due with this response are being submitted herewith. If any additional fees *necessary* to keep the present case pending and/or to protect the filing date are due, or any overpayment has been made, authorization is hereby given to charge or credit Deposit Account No. 02-2095 for any deficiencies or overages in connection with this response. No authorization is permitted to charge "optional" fees, e.g., excess claims fees.

Respectfully submitted,

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